

26. (New) A composition according to Claim 24, and having the components of Example 2 as follows:

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Component	Weight (mg)
Compound of Formula 1 as defined in Claim 1	60
GDO/GMO (8:2)	200
Propylene Glycol	100
Lecithin	20
Na Deoxycholate	0.5
Glycerine	2.4
Methyl paraben	1.8
Propyl paraben	0.2
Water	q.s.

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#### REMARKS

Claims 1-26 are in the application.

Claims 1-23 stand rejected under 35 USC 103(a) as being unpatentable over Romines et al, U.S. Patent 5 852 195, and Suzuki et al, U.S. Patent 5 693 337.

Entry of the amendments under 37 CFR 116(b) is deemed appropriate because they either render the amended claims patentable over the prior art or place them in better condition for consideration upon appeal.

Reconsideration of this application is respectfully requested.

#### THE REJECTION UNDER 35 USC 103(a)

Claim 14 has been amended so that it corresponds to the specification, page 5, lines 14-15.

This rejection is again traversed because Claims 1-23, as well as new Claims 24, 25 and 26, are patentably distinguishable over the combination of U.S. Patent 5 852 195 (the '195 patent) and U.S. Patent No. 5 693 337 (the '337

patent) because the Examiner has failed to make out a *prima facie* case of obviousness.

The Examiner admits that the '195 patent and the '337 patent together do not teach:

(1) the particular mixture of mono-, di- and triglyceride or

(2) weight ratio of the pyranone compound of Formula I in the emulsion.

Further, the Examiner fails to note that the monoglyceride and diglyceride recited are mono- and di- unsaturated fatty acid esters of glycerol having sixteen to twenty-two carbon atom chain length and the triglyceride is a saturated fatty acid ester of glycerol having six to twelve carbon atoms. The '337 patent fails to appreciate this limitation as can be gleaned by the description of the oil phase in column 4, lines 54-63, wherein it is stated:

The "oil component" used in the present invention may be, for instance, vegetable oils and/or synthetic or semisynthetic glycerides. Examples of vegetable oils are soybean oil, sesame oil, cottonseed oil, rapeseed oil, orange oil, corn oil and olive oil. The synthetic or semisynthetic glyceride is not restricted to specific ones, but examples thereof in general include mono-, di- or triglycerides whose acid components are C<sub>6</sub> to C<sub>20</sub> saturated and/or unsaturated fatty acids and mixtures comprising at least two members of these glycerides.

Suzuki et al does not distinguish between using unsaturated or saturated fatty acid esters and does not teach or suggest using unsaturated fatty acid esters for the mono- and diglycerides and saturated fatty acids for triglycerides. A *prima facie* case requires a teaching in the art to provide motivation to change prior art to render a limitation obvious and not unsupported assertions by the Examiner.

The Examiner further asserts in the second full paragraph on page 5 of the Office Action,

"Note that the incorporation of a known pharmaceutical active in an emulsion employing known excipients and

pharmaceutical auxiliaries is within the purview of the skilled artisan."

While this assertion as a generality may have some credence, it does not constitute a *prima facie* case of obviousness against a formulation consisting of carefully selected unobvious combinations of components.

Claims dependent from Claim 1 are patentably distinguishable over the combination of the '337 and '195 patents for the reasons that Claim 1 is and because of the additional limitations recited in the dependent claims. Claims 22 and 23 additionally do not read on compositions that contain either citric acid, amino acids or their pharmaceutically acceptable salts.

New Claim 24 is directed to a submicron lipid emulsion pharmaceutical composition comprising

(a) a therapeutically effective amount of the compound of Formula I,

(b) a mixture of diglyceride and monoglyceride in a ratio of about 8:2 (diglyceride : monoglyceride) by weight, wherein the monoglycerides are mono- and di- unsaturated fatty acid esters of glycerol having sixteen to twenty-two carbon atom chain length;

(c) an emulsifying agent consisting of lecithin; and

(d) a liquid phase comprising one or more pharmaceutically acceptable solvents.

Support for new Claim 24 can be found in the specification, page 5, lines 14 and 15, and in original Claim 14. Therefore, Claim 24 does not introduce new matter into the application. New Claim 24 is patentably distinguishable over the combination of the '337 patent and the '195 patent for the reasons set forth in the discussion of the rejection of Claim 1, as well as for the requirement that the ratio of diglyceride to monoglyceride be 8:2 by weight.

The ratio of 8:2 results in a particle size that is much smaller than the particle size when the 8:2 ratio is not used.

While the Examiners observation with respect to smaller particle size has merit, that fact does not teach or suggest to one skilled in the art that the use of a mixture of diglyceride and monoglyceride in a ratio of about 8:2 (diglyceride:monoglyceride) would result in the creation of particles much smaller than the the use of other ratios of diglyceride to monoglyceride. This much smaller particle size provides a pharmaceutical composition with enhanced oral bioavailability, prolonged blood levels and greater safety.

New Claim 25 limits the composition of Claim 24 to an oral or parenteral composition and, hence, it is patentably distinguishable over the combination of the '337 patent and the '195 patent for the same reason that Claim 24 is.

New Claim 26 limits the composition of Claim 24 to one containing specific components and does not include citric acid, amino acids or pharmaceutically acceptable salts thereof, and is patentably distinguishable over the combination of the '337 patent and the '195 patent for that reason, as well as for the reasons set forth in the discussion of the rejection of Claim 24.

Favorable consideration is respectfully solicited.

Respectfully submitted,

  
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Sidney B. Williams, Jr.

SBW/smd

FLYNN, THIEL, BOUTELL & TANIS, P.C. 2026 Rambling Road Kalamazoo, MI 49008-1699 Phone: (269) 381-1156 Fax: (269) 381-5465	Dale H. Thiel David G. Boutell Ronald J. Tanis Terryence F. Chapman Mark L. Maki David S. Goldenberg Sidney B. Williams, Jr. Liane L. Churney Brian R. Tumm Tricia R. Cobb	Reg. No. 24 323 Reg. No. 25 072 Reg. No. 22 724 Reg. No. 32 549 Reg. No. 36 589 Reg. No. 31 257 Reg. No. 24 949 Reg. No. 40 694 Reg. No. 36 328 Reg. No. 44 621
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Encl: Marked-Up Amended Claims 14, 22 and 23

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14. (Amended) A pharmaceutical composition of  
~~e~~Claim 1, wherein the oil component is a mixture of  
diglyceride and monoglyceride in a ratio of ~~from~~ about  
8:2 (diglyceride : monoglyceride) by weight.

22. (Amended) A submicron lipid emulsion  
pharmaceutical composition selected from the group  
consisting of a composition comprising of Example 1 as  
follows:

Component	Weight (mg)
Compound of Formula 1 as defined in Claim 1	60
Triglyceride	200
Propylene Glycol	100
Lecithin	20
Na Deoxycholate	0.5
Glycerine	24
Methyl paraben	1.8
Propyl paraben	0.2
Water	q.s.

And a composition comprising of Example 2 as  
follows:

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Component	Weight (mg)
Compound of Formula 1 as defined in Claim 1	60
GDO/GMO (8:2)	200
Propylene Glycol	100
Lecithin	20
Na Deoxycholate	0.5
Glycerine	2.4
Methyl paraben	1.8
Propyl paraben	0.2
Water	q.s.

23. (Amended) A submicron liquid emulsion pharmaceutical composition selected from the group consisting of a composition comprising of Example 3 as follows:

Component	Weight (mg)
Compound of Formula 1 as defined in Claim 1	60
GDO	200
Propylene Glycol	100
Lecithin	20
Na Deoxycholate	0.5
Glycerine	2.4
Methyl paraben	1.8
Propyl paraben	0.2
Water	q.s.

and a composition comprising of Example 5 as follows:

Component	Weight (mg)
Compound of Formula 1 as defined in Claim 1	60
MCT/GDO (8:2)	200
Lecithin	20
BHT	0.1
Glycerine	2.4
Water	q.s.